Sleep Medicine 15 (2014) 880–886

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Elimination of central sleep apnea by cardiac valve replacement: a continuous follow-up study in patients with rheumatic valvular heart disease

Ning Ding [a], Bu-Qing Ni [b], Xi-Long Zhang [a], Wang-Jian Zha [a], Sean Z. Hutchinson [c], Wei Lin [d], Mao Huang [a], Shi-Jiang Zhang [b,*], Hong Wang [a,*]

[a] Department of Respiratory Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China
[b] Department of Cardiothoracic Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China
[c] Morsani College of Medicine, Tampa, FL, USA
[d] Department of Geriatric Medicine, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

ARTICLE INFO

Article history:
Received 10 October 2013
Received in revised form 10 February 2014
Accepted 13 February 2014
Available online 17 May 2014

Keywords:
Sleep-disordered breathing
Rheumatic valvular heart disease
Central sleep apnea
Obstructive sleep apnea
Cardiac valve replacement
Cardiac function

ABSTRACT

Background: Recent studies have suggested that cardiac surgery may affect sleep-disordered breathing (SDB) in chronic heart failure patients. However, the dynamic changes in sleep apnea and heart function after cardiac surgery and the mechanisms responsible for these changes remain unknown.
Methods: Patients with rheumatic valvular heart disease (RVHD) and SDB were enrolled and followed up at three, six and 12 months after cardiac valve replacement (CVR). Baseline and follow-up clinical data consisting of NYHA classification, 6 min walk distance (6-MWD), medications, echocardiography, electrocardiography, chest X-ray, arterial blood gas, lung-to-finger circulation time (LFCT), and sleep data were collected and evaluated.
Results: Twenty-four central sleep apnea (CSA) patients and 15 obstructive sleep apnea (OSA) patients completed three follow-up assessments. Comparison of the baseline parameters between OSA patients and CSA patients showed that CSA patients had a worse baseline cardiac function assessed by higher NYHA class, shorter 6-MWD, larger left atrial diameter, longer LFCT, and enhanced chemosensitivity (higher pH and lower arterial carbon dioxide tension ($PaCO_2$)). A continuous significant elevation in 6-MWD and left ventricular ejection fraction and decrease in NYHA class, plasma BNP, and left atrial diameter were found in both CSA and OSA patients. When comparing CSA and OSA patients, the CSA indices were remarkably reduced at month 3 post CVR and sustained throughout the trial, whereas there were no significant decreases in OSA index and hypopnea index. pH values and LFCT were markedly decreased and $PaCO_2$ markedly increased in patients with CSA at the end of the third months following CVR. These changes were sustained until the end of the trial.
Conclusions: CSA patients with RVHD had a worse baseline cardiac function, enhanced chemosensitivity and disordered hemodynamic as compared with OSA patients with RVHD. CSA were eliminated after CVR; however, there were no changes in OSA. The elimination of CSA, post CVR, is associated with the combined efficacies of improvement of cardiac function, normalized chemosensitivity, and stabilized hemodynamic.

1. Introduction

Sleep-disordered breathing (SDB) may be classified into central sleep apnea (CSA) and obstructive sleep apnea (OSA). SDB, especially CSA, occurs frequently in patients with chronic heart failure (CHF). One large-scale study showed that SDB was present in 76% (40% CSA, 36% OSA) of patients with symptomatic CHF [1]. Of the two types of sleep apnea, studies have shown that OSA is implicated as a cardiovascular risk factor, and that CSA is an end-result of deteriorating cardiac function [2–5].

Several case reports strongly suggest that heart valve repair or replacement may lead to improvements in SDB [6–9]. Tomcsanyi and Yasuma reported that CSA events were substantially reduced after successful cardiac valve replacement (CVR) [7,9], and Collop

* Corresponding authors. Address: Department of Cardiothoracic Surgery, The First Affiliated Hospital of Nanjing Medical University, Guangzhou 300 Road, Nanjing 210029, China. Tel./fax: +86 02583673066 (S.-J. Zhang).
E-mail address: shijiangzhang@hotmail.com (S.-J. Zhang).

http://dx.doi.org/10.1016/j.sleep.2014.02.007
1389-9457/

and Mansfield found an improvement in CSA after successful heart transplant [10,11]. Abe [12] investigated 74 patients with valvular heart disease and reported significant improvements in CSA index (CSAI), pulmonary capillary wedge pressure (PCWP), and mean pulmonary artery pressure (PAP), and no changes in OSA index (OSAI) 14 days post heart-valve repair.

Although heart valve treatment has been reported to eliminate CSA or cause a shift from CSA to OSA, the mechanisms responsible for these effects are not fully understood. Some researchers [8,13–17] have suggested that the decrease in CSA may be related to enhanced lower partial pressure of arterial CO_2 ($PaCO_2$) and reduced lung-to-ear circulation time, whereas others [12] have considered that the improvements in CSA or shift from CSA to OSA may be the result of improved cardiac function.

In our previous study, we demonstrated that 38.8% of patients with rheumatic valvular heart disease (RVHD) also suffered from SDB [18]. We hypothesized that CVR surgery may affect CSA and OSA in patients with RVHD and SDB, and that the changes in SDB may be due to an improvement of heart function, chemosensitivity and hemodynamic circulation. In the current prospective study, we therefore investigated the dynamic changes in the various parameters at three, six, and 12 months after heart valve surgery in patients with RVHD and SDB.

2. Methods

2.1. Subjects and study design

Data were collected from 262 patients with RVHD who were admitted to the Cardiothoracic Surgery Department for CVR. The inclusion criteria were: (i) age 18–70 years; (ii) symptomatic stable heart failure, New York Heart Association (NYHA) class ⩾II despite optimal drug therapy; (iii) diagnosis of RVHD based on the 2004 World Health Organization (WHO) criteria for the diagnosis of rheumatic fever and rheumatic heart disease [19]; (iv) indications for valvular replacement surgery met the American College of Cardiology/American Heart Association (ACC/AHA) 2008 update guidelines for the management of patients with valvular heart disease [20]; and (v) patients combined with SDB (apnea–hypopnea index (AHI) ⩾10/h) according to the results of polysomnography (PSG).

The diagnosis of RVHD was based on the 2004 WHO criteria for the diagnosis of rheumatic fever and rheumatic heart disease [19]: a primary episode of rheumatic fever or a clinical rheumatic heart disease features currently, with typical rheumatic valvular lesions examined by Doppler echocardiography.

The indications for valvular replacement surgery were based on ACC/AHA 2008 update guidelines for the management of patients with valvular heart disease [20], including: (i) symptomatic patients with moderate to severe mitral stenosis or regurgitation; (ii) symptomatic patients with chronic moderate to severe aortic stenosis or regurgitation, and left ventricular systolic dysfunction (ejection fraction ⩽0.50) at rest; and (iii) decompensated heart failure with moderate to severe valvular lesions involved in at least two cardiac valves.

A PSG test was performed 1–7 (3.7 ± 1.6) days before CVR for each patient. According to the results of PSG, 70 patients were combined with SDB (48 patients with CSA (CSAI >50% AHI) and 22 patients with OSA (OSAI >50% AHI)). Of these, 39 patients (24 with CSA; 15 with OSA) successfully completed three follow-up assessments (three, six, and 12 months after CVR surgery) between April 2010 and January 2013.

This study was approved by the Institutional Patient Ethics Committee (IPEC approval #20092801) and registered on ClinicalTrials.gov (#NCT01426776). All patients gave written informed consent prior to study participation.

2.2. Baseline and follow-up assessments

Patients received optimal drug therapies (including digoxin, diuretics, nitrates, angiotensin-converting enzyme inhibitors, and β-blockers) to obtain a stable clinical status. Demographics and clinical data including age, sex, height, weight, body mass index (BMI), Epworth Sleepiness Scale (ESS) score, and medication use were prospectively entered into a dedicated database. All patients underwent standard clinical evaluations including New York Heart Association (NYHA) class, plasma brain natriuretic peptide (BNP), echocardiography, electrocardiography, arterial blood gas and lung-to-finger circulation time (LFCT). In addition, a 6 min walk distance (6-MWD) was performed within the first three days of hospital admission, according to American Thoracic Society guidelines [21]. 6-MWD was not performed in patients whose lower limb joints had been damaged by rheumatic fever.

Follow-up assessments of medications, BMI, blood pressure, NYHA class, plasma BNP, ESS score, echocardiography, electrocardiography, arterial blood gas, LFCT, 6-MWD, and sleep parameters were repeated three, six and, 12 months after CVR.

2.3. Polysomnography

The sleep study was performed by unattended overnight PSG (Embla S4500 System, Broomfield, CO, USA) as described previously [18]. Sleep was monitored using 5 electroencephalographic

Table 1
Baseline characteristics of the patients.

	CSA patients (n = 24)	OSA patients (n = 15)	t/χ^2	P
Age (years)	53.5 ± 8.9	51.4 ± 9.9	0.781	0.440
Sex			2.134	0.144
Male	12 (50.0)	11 (73.3)		
Female	12 (50.0)	4 (26.7)		
AF	20 (83.3)	4 (26.7)	12.945	0.000
BMI (kg/m^2)	22.8 ± 3.0	26.2 ± 4.3	2.972	0.005
6-MWT (m)	264.9 ± 77.4	320.9 ± 74.8	2.209	0.034
BNP (pg/mL)	605.6 ± 200.7	503.7 ± 103.5	2.058	0.047
ESS score	12.8 ± 5.8	11.5 ± 5.8	0.690	0.494
NYHA class			13.225	0.000
I	0 (0)	4 (26.7)		
II	8 (33.3)	9 (60.0)		
III	16 (66.7)	2 (13.3)		
Echocardiography				
LVEF (%)	58.8 ± 6.6	61.4 ± 6.3	1.200	0.238
LVDd (mm)	54.8 ± 10.0	55.4 ± 8.2	0.198	0.844
LVDs (mm)	37.7 ± 8.8	37.1 ± 7.2	0.222	0.825
LAD (mm)	55.4 ± 10.9	46.9 ± 13.5	2.158	0.038
PSG				
AHI (/h)	25.4 ± 13.0	21.5 ± 8.6	1.037	0.306
OSAI (/h)	3.3 ± 2.9	15.7 ± 7.0	7.715	0.000
CSAI (/h)	19.2 ± 10.0	2.2 ± 2.5	6.433	0.000
HI (/h)	2.9 ± 2.0	3.5 ± 2.6	0.848	0.402
Mean SpO_2 (%)	95.1 ± 1.4	95.6 ± 1.3	0.830	0.412
Minimal SpO_2 (%)	84.3 ± 5.8	81.1 ± 5.3	1.772	0.085
ODI (/h)	19.7 ± 16.4	12.7 ± 7.4	1.534	0.134
Sleep efficiency (%)	63.4 ± 7.4	67.1 ± 8.8	1.394	0.172
Awake arterial blood gases				
pH	7.447 ± 0.026	7.434 ± 0.034	1.315	0.197
PaO_2 (mmHg)	80.1 ± 13.7	81.2 ± 7.7	0.276	0.784
$PaCO_2$ (mmHg)	38.5 ± 5.3	43.7 ± 2.5	3.559	0.001
LFCT (s)	29.0 ± 6.7	18.5 ± 3.9	5.491	0.000

AF, atrial fibrillation; BMI, body mass index; 6-MWD, 6 min walk distance; NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LAD, left atrial diameter; AHI, apnea/hypopnea index; CSAI, central sleep apnea index; OSAI, objective sleep apnea index; ESS, Epworth Sleepiness Scale; HI, hypopnea index; SpO_2, pulse oxygen saturation; ODI, oxygen desaturation index; PaO_2, arterial oxygen tension; $PaCO_2$, arterial carbon dioxide tension.
Data are presented as no. (%) or mean ± SD.

Table 2
Follow-up values in central sleep apnea patients.

	Baseline	3 months	6 months	12 months	*F*	*P*
BMI (kg/m^2)	22.8 ± 3.0	23.1 ± 2.7	23.8 ± 2.8	23.6 ± 2.1	2.959	0.090
NYHA class	3.67 ± 0.48	2.38 ± 0.58*	1.73 ± 0.63*,#	1.65 ± 0.70*,#	48.572	0.000
6MWT (m)	264.9 ± 77.4	413.3 ± 77.9*	438.6 ± 60.3*,#	446.3 ± 70.3*,#	26.266	0.000
BNP (pg/mL)	605.6 ± 200.7	406.8 ± 83.2*	415.7 ± 86.1*	288.6 ± 103.5*,#,§	17.042	0.000
ESS score	12.8 ± 5.8	7.0 ± 4.4*	7.9 ± 4.7*	6.2 ± 4.1*	9.175	0.002
LVEF (%)	58.8 ± 6.6	60.4 ± 7.0	60.7 ± 5.4	64.8 ± 4.0*,#,§	5.165	0.011
LVEDd (mm)	54.8 ± 10.0	50.6 ± 9.6*	50.6 ± 8.9*	47.4 ± 5.4*,#,§	12.403	0.000
LVEDs (mm)	37.7 ± 8.8	34.2 ± 8.6*	34.2 ± 7.8*	30.9 ± 4.9*,#,§	10.573	0.001
LAD (mm)	55.4 ± 10.9	49.3 ± 10.7*	47.8 ± 11.0*	44.1 ± 9.4*,#,§	17.686	0.000
AHI (/h)	25.4 ± 13.0	11.3 ± 11.3*	8.3 ± 7.2*	7.2 ± 5.7*	19.216	0.000
OSAI (/h)	3.3 ± 2.9	2.4 ± 3.7	3.0 ± 4.6	1.9 ± 2.0	2.382	0.240
CSAI (/h)	19.2 ± 10.0	0.43 ± 1.4*	0.27 ± 1.3*	0.24 ± 0.75*	40.526	0.000
HI (/h)	2.9 ± 2.0	8.5 ± 9.6	5.0 ± 3.8	5.1 ± 4.5	2.670	0.091
Mean SpO_2 (%)	95.1 ± 1.4	95.2 ± 1.5	95.6 ± 0.3	95.6 ± 1.6	3.200	0.059
Minimum SpO_2 (%)	84.3 ± 5.8	86.3 ± 4.9	85.6 ± 8.0	84.3 ± 7.2	1.234	0.337
ODI (/h)	19.7 ± 16.4	10.1 ± 9.6	8.2 ± 7.1	6.2 ± 5.3*	9.101	0.002
Sleep efficiency (%)	63.4 ± 7.4	72.1 ± 7.2*	71.6 ± 8.4*	73.7 ± 8.0*	7.585	0.004
pH	7.447 ± 0.026	7.435 ± 0.024*	7.425 ± 0.021*	7.413 ± 0.023*,#	10.887	0.001
$PaCO_2$ (mmHg)	38.5 ± 5.3	42.1 ± 2.8*	42.8 ± 2.9*	43.3 ± 3.9*	5.418	0.004
PaO_2 (mmHg)	80.1 ± 13.7	88.3 ± 11.7*	90.1 ± 11.9*	92.9 ± 13.3*	5.459	0.012
LFCT (s)	29.0 ± 6.7	20.3 ± 4.3*	17.5 ± 2.4*	17.2 ± 3.7*	14.009	0.000

BMI, body mass index; NYHA, New York Heart Association; 6-MWD, 6 min walk distance; BNP, brain natriuretic peptide; ESS, Epworth Sleepiness Scale; LVEF, left ventricle ejection fraction; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LAD, left atrial diameter; AHI, apnea/hypopnea index; OSAI, obstructive sleep apnea index; CSAI, central sleep apnea index; HI, hypopnea index; SpO_2, pulse oxygen saturation; ODI, oxygen desaturation index; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; LFCT, lung-to-finger circulation time.
Data were analyzed by repeated-measures analysis of variance and expressed as mean ± SD.
* Indicates there is a statistical difference among baseline and three follow-ups.
# Indicates there is a statistical difference when the follow-ups of 6 or 12 months compared with the follow-ups of 3 months.
§ Indicates there is a statistical difference between the follow-ups of 6 months and 12 months.

Table 3
Follow-up values in obstructive sleep apnea patients.

	Baseline	3 months	6 months	12 months	*F*	*P*
BMI (kg/m^2)	26.2 ± 4.3	25.3 ± 2.7	25.3 ± 2.9	25.3 ± 2.8	1.194	0.353
NYHA class	2.87 ± 0.64	2.07 ± 0.59*	1.60 ± 0.51*,#	1.33 ± 0.49*,#	28.368	0.000
6MWT (m)	320.9 ± 74.8	424.3 ± 50.4*	464.0 ± 49.1*,#	488.0 ± 51.2*,#,§	59.413	0.000
BNP (pg/mL)	503.7 ± 107.5	365.4 ± 83.2*	338.4 ± 43.7*	276.6 ± 61.0*,#,§	21.163	0.000
ESS score	11.5 ± 5.8	10.4 ± 4.4	9.8 ± 4.2	9.3 ± 3.6	1.807	0.200
LVEF (%)	61.4 ± 6.3	62.7 ± 3.8	63.7 ± 3.8	64.6 ± 4.4*,#	4.153	0.031
LVEDd (mm)	55.4 ± 8.2	52.6 ± 8.2*	51.5 ± 7.3*	49.6 ± 7.1*,#,§	14.024	0.006
LVEDs (mm)	37.1 ± 7.2	35.2 ± 6.6*	34.1 ± 6.0*	32.9 ± 5.8*,#,§	9.245	0.002
LAD (mm)	46.9 ± 13.5	41.4 ± 7.8*	39.5 ± 7.9*	37.8 ± 6.6*,#	18.542	0.000
AHI (/h)	21.5 ± 8.6	20.2 ± 9.0	19.3 ± 8.2	18.7 ± 7.2	1.110	0.383
OSAI (/h)	15.7 ± 7.0	16.0 ± 7.6	15.4 ± 6.3	14.7 ± 4.8	0.370	0.766
CSAI (/h)	2.2 ± 2.5	0.53 ± 0.74*	0.47 ± 0.92*	0.40 ± 0.63*	5.094	0.017
HI (/h)	3.5 ± 2.6	3.7 ± 3.5	3.5 ± 2.5	3.7 ± 4.2	0.030	0.993
Mean SpO_2 (%)	95.6 ± 1.3	95.2 ± 1.2	95.6 ± 1.4	95.8 ± 1.2	1.381	0.296
Minimal SpO_2 (%)	81.1 ± 5.3	79.4 ± 5.2	81.8 ± 4.6	82.8 ± 4.7	3.166	0.064
ODI (/h)	12.7 ± 7.4	14.1 ± 4.9	13.0 ± 4.8	12.7 ± 4.1*	1.875	0.188
Sleep efficiency (%)	67.1 ± 8.8	68.5 ± 5.2*	70.5 ± 7.5*	69.9 ± 7.5*	1.773	0.206
pH	7.434 ± 0.034	7.425 ± 0.024	7.420 ± 0.017	7.421 ± 0.019	1.105	0.385
$PaCO_2$ (mmHg)	43.7 ± 2.5	42.7 ± 2.0	43.1 ± 2.2	42.7 ± 2.9	1.572	0.247
PaO_2 (mmHg)	81.2 ± 7.7	85.7 ± 5.9*	88.0 ± 5.3*	90.1 ± 5.9*	6.854	0.006
LFCT (s)	18.5 ± 3.9	15.6 ± 2.6	16.9 ± 2.9	16.1 ± 2.9	2.669	0.082

BMI, body mass index; NYHA, New York Heart Association; 6-MWD, 6 min walk distance; BNP, brain natriuretic peptide; ESS, Epworth Sleepiness Scale; LVEF, left ventricle ejection fraction; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LAD, left atrial diameter; AHI, apnea/hypopnea index; OSAI, obstructive sleep apnea index; CSAI, central sleep apnea index; HI, hypopnea index; SpO_2, pulse oxygen saturation; ODI, oxygen desaturation index; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; LFCT, lung-to-finger circulation time.
Data were analyzed by repeated-measures analysis of variance and expressed as mean ± SD.
* Indicates there is a statistical difference among baseline and three follow-ups.
# Indicates there is a statistical difference when the follow-ups of 6 or 12 months compared with the follow-ups of 3 months.
§ Indicates there is a statistical difference between the follow-ups of 6 months and 12 months.

channels (EEG; F4–M1, C4–M1, O2–M1, E12–M2, and E2–M2) and a submental electromyogram. Nasal airflow was measured by continuously recording the nasal pressure, snoring, pulse oximetry, and body position, as well as chest and abdominal effort. Analyses were performed by two physicians who specialized in SDB but who were not directly involved in this study.

The 2012 standards of American Academy of Sleep Medicine were used for scoring sleep apnea types and associated events [22]; obstructive apnea: complete cessation of airflow with continued paradoxical chest and abdominal excursion for ⩾10 s; central apnea: complete cessation of airflow as well as complete cessation of chest and abdominal excursion ⩾10 s; hypopnea: reduction of

airflow >50% baseline lasting ⩾10 s and associated with ⩾4% desaturation. The AHI was defined as the number of apneas and hypopneas per hour of sleep. Although AHI ⩾5/h was considered a diagnostic criterion of sleep apnea syndrome, we chose AHI ⩾10/h because: (i) a higher AHI population was needed to investigate the effect of surgery on SDB; and (ii) AHI ⩾10 has been set as a recruitment criterion for SDB investigation in other studies [23–25]. SBD in which >50% of events, were central was defined as CSA; if >50% of events were obstructive, it was defined as OSA.

2.4. Lung-to-finger circulation time

Lung-to-finger circulation time (LFCT) was measured instead of lung-to-ear circulation time [17,26] because the SpO_2 in our patients was assessed by a finger rather than an ear. LFCT was measured from the onset of the first breath after an apnea to the nadir of the subsequent dip of SpO_2. Mean values were obtained for each of these variables from three consecutive hyperpnea–apnea cycles during stage 2 sleep in each patient. The delay of LFCT could reflect the prolonged lung-to-carotid body circulation time.

2.5. Statistical analysis

Study population characteristics were expressed as mean ± standard deviation and counts (with percentages). Frequencies of parameters were analyzed by χ^2 or Fisher's exact tests. Baseline comparison between patients with CSA and OSA was performed by *t*-test for independent variables. Analysis of variance (ANOVA) of repeated measures was performed to detect significant differences between the follow-up groups. If the Mauchly test of sphericity was not satisfied, the Greenhouse–Geisser adjustment result was used. Bonferroni's adjustment was used for multiple comparisons. Data were analyzed using SPSS 13.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

Of 39 patients who completed follow-up assessments, there were 24 with CSA and 15 with OSA. The comparison of clinical and sleep parameters baselines is shown in Table 1. There were no significant differences in age, LVEF, ESS score, AHI, mean SpO_2, minimum SpO_2, sleep efficiency, or PaO_2 between the CSA and OSA patients. Compared with the OSA patients, CSA patients experienced a higher prevalence of atrial fibrillation, higher NYHA class, lower BMI, shorter 6-MWD, larger left atrial diameter (LAD), lower $PaCO_2$, and longer LFCT.

The follow-up results for patients with CSA and OSA are shown in Tables 2 and 3, respectively. There were no changes in BMI in both groups during the three follow-up visits. NYHA class and plasma BNP decreased continuously and 6-MWD increased continuously in both CSA and OSA patients (Fig. 1). Continuously significant increase in LVEF and decrease in LAD, left ventricular diastolic dimension, and left ventricular systolic dimension were found in both CSA and OSA patients. In both CSA and OSA patients, CSAI were remarkably reduced three months following CVR and sustained throughout the trial, whereas there were no significant decreases in OSAI and hypopnea index (HI) (Fig. 2). pH values and LFCT were markedly decreased and $PaCO_2$ were markedly increased in patients with CSA three months following CVR. These changes were sustained until the end of the trial. In contrast, there

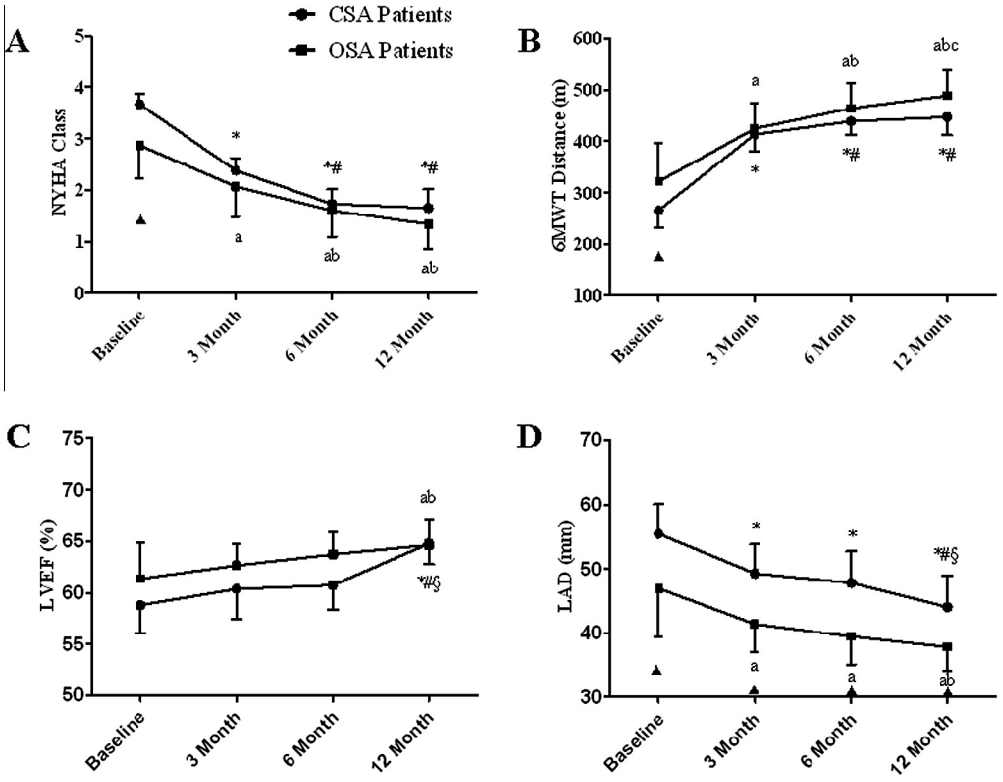

Fig. 1. Clinical changes in central sleep apnea (CSA) and obstructive sleep apnea (OSA) patients following cardiac valve replacement (CVR). Symbols (∗, #, and §) indicate significant differences among baseline and three follow-ups in CSA patients, and letters (a, b, and c) indicate significant differences among baseline and three follow-ups in OSA patients; ▲, significant difference between CSA and OSA patients at the same follow-up (as in Figs. 2 and 3). New York Heart Association (NYHA) class decreased (A) and 6 min walk distance (6-MWD) increased (B) continuously in both CSA and OSA patients. However, OSA patients had a higher NYHA class and longer 6-MWD than CSA patients at baseline. Left ventricular ejection fraction (LVEF) was significantly increased and left atrial diameter was significantly decreased during three follow-ups in both CSA and OSA patients (C and D). CSA patients had larger left atrial diameter than OSA patients at baseline and follow-up (D).

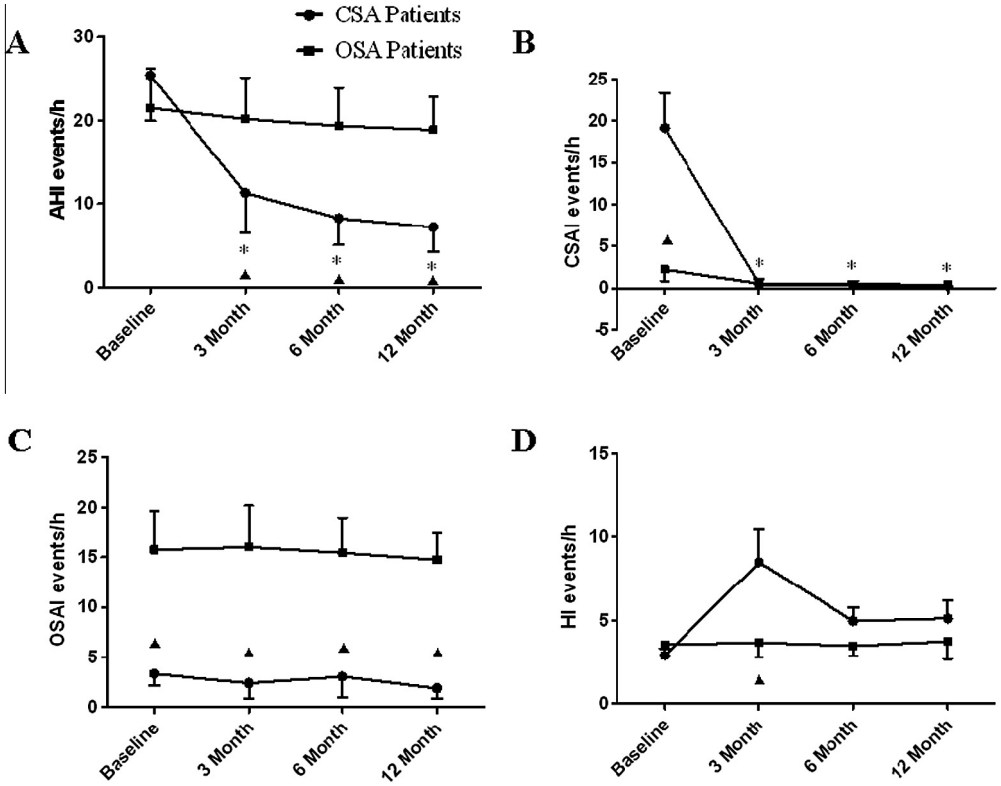

Fig. 2. Polysomnography results for central sleep apnea (CSA) and obstructive sleep apnea (OSA) patients. Apnea–hypopnea index (AHI) was reduced markedly in CSA patients three months following cardiac valve replacement and sustained throughout the trial (A). CSA index (CSAI) was reduced markedly in both CSA and OSA patients during the first follow-up (B). OSA index (OSAI) and hypopnea index (HI) did not differ significantly between baseline and follow-ups in either CSA or OSA patients (C and D).

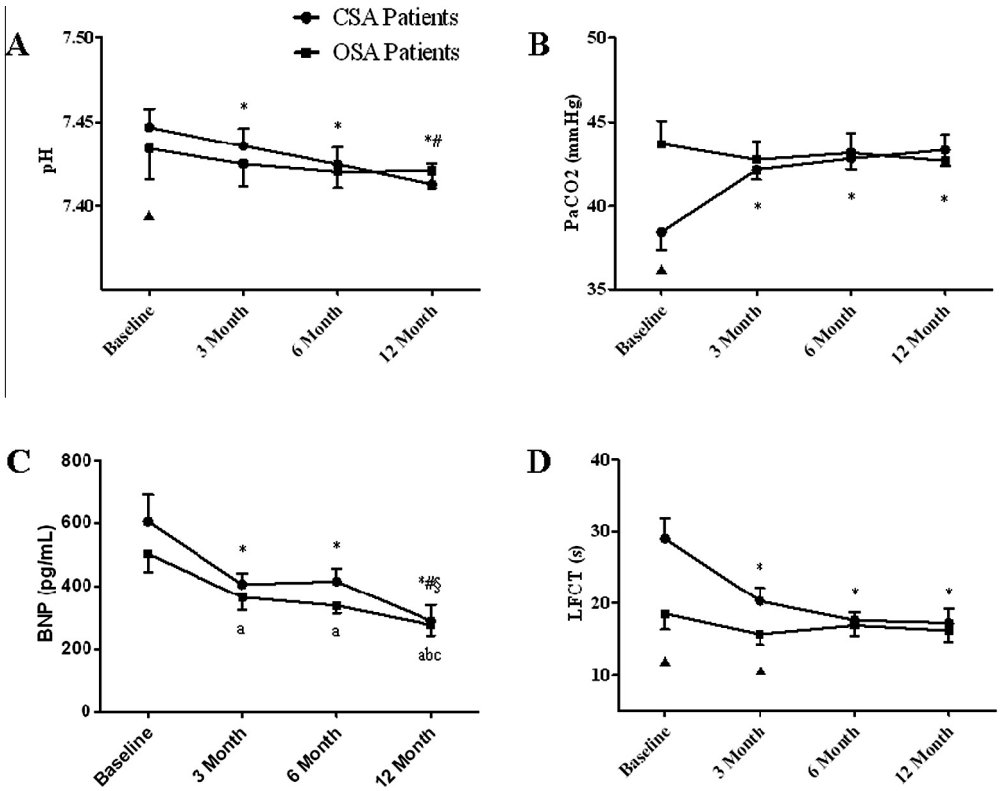

Fig. 3. Hematologic parameters in central sleep apnea (CSA) and obstructive sleep apnea (OSA) patients. CSA patients had higher pH, lower arterial carbon dioxide tension ($PaCO_2$) and longer lung-to-finger circulation time (LFCT) at baseline, compared with OSA patients (A, B, and D). pH and LFCT were significantly reduced and $PaCO_2$ was significantly elevated during the first follow-up in CSA patients, but there were no changes in these parameters in OSA patients (A, B, and D). Plasma brain natriuretic peptide (BNP) levels fell continuously in both CSA and OSA patients (C).

were no significant differences in pH, $PaCO_2$ and LFCT among baseline, and three follow-ups in patients with OSA (Fig. 3).

4. Discussion

There were no differences in the severity of SDB between CSA and OSA patients. However, compared with OSA patients, CSA patients had worse baseline heart function (represented by NYHA class, plasma BNP, 6-MWD and LAD), as well as enhanced chemosensitivity (represented by blood gas) and disordered hemodynamics (represented by LFCT). In addition, there was also a higher prevalence of atrial fibrillation in CSA patients. These findings were in accordance with the results of previous studies [1,23,27]. Our results support the viewpoint that CSA is a consequence of heart failure, since improvement of heart failure following CVR surgery almost eliminated CSA in our patients.

The mechanism for the disappearance of CSA after cardiac surgery is still a subject of controversy. It was shown in earlier studies that enhanced sensitivity to CO_2 and reduced $PaCO_2$ contributed to the development of CSA [13–16]. Recent studies demonstrated that most CSA patients might have circulation delay [6,8]. Other studies also connect pathogenesis of CSA with loop gain theory [28], an indicator for the severity of ventilatory instability. However, Abe [12] and Ryan [26] documented that the improvements in CSA or the shift from CSA to OSA in heart failure patients was associated with improved left ventricular systolic function, assessed by LVEF.

Taking these possible influential factors into consideration, it was observed in this study that three months following CVR the three major factors (cardiac function, chemosensitivity, and hemodynamic) were all markedly improved in CSA patients. We considered that the elimination of CSA was not attributed to one particular independent factor, but rather it may be that the combined effects of the three factors played a synergistic role in the elimination of CSA. Among the three factors, cardiac dysfunction should be the primary factor as, when cardiac function had improved, the correction of enhanced chemosensitivity and disordered hemodynamics could be followed. However, the importance of chemosensitivity should not be neglected because the occurrence of CSA is closely associated with hypocapnia and respiratory alkalosis [13–16]. Observed from the three follow-ups post cardiac surgery, we detected that the trend of CSA disappearance kept pace with the trend of improvement in $PaCO_2$, pH, and LFCT: normalized in three months and sustained at the improved level to the end of trial (Fig. 3). Mansfield [11] found that CHF patients with CSA who underwent heart transplantation experienced persistent CSA despite normalization of heart function and sympathetic activity. He postulated that mechanisms other than heart dysfunction and heightened sympathetic activation are likely responsible for the development of CSA persistence. By analyzing the pre- and post-cardiac surgical data from Mansfield's study it can be seen that CSA patients had lower $PaCO_2$ and higher pH level compared with non-CSA patients. In our study, the abnormalities of chemosensitivity appear to reflect the persistence of CSA.

Although our CSA and OSA patients showed that their CSA events almost disappeared following CVR, there were no significant decreases in both OSA and related hypopnea events. This phenomenon could be the associated pathogenesis of OSA, which is possibly related to upper airway collapse or obstruction resulting from obesity, anatomic narrowness, and so on. However, CVR could not resolve the aforementioned abnormalities in OSA patients.

From the three successive follow-ups at three, six, and 12 months post CVR, we found that at the third month following surgery, a marked improvement was achieved in parameters of cardiac function, blood gas, and PSG. The extent of the improvements mentioned above became significantly smaller after the initial three months, suggesting that the critical recovery period for our CSA patients is the first three months after CVR.

However, there are some potential limitations to our study. Although a previous study [12] found that the severity of CSAI was correlated with PAP and PCWP, we were unable to obtain this relational data because all the patients refused invasive examinations. Additionally, several studies [6,26] have shown that CSA shifted to OSA after cardiac surgery or CANPAP (Canadian Positive Airway Pressure Trial for Heart Failure Patients with Central Sleep Apnea) treatment; however, we did not observe this phenomenon. Although we found that OSA still existed while CSA almost disappeared after CVR, it was difficult to ascertain whether the postoperative OSA events belonged to their baseline OSA events or to the newly converted OSA events (from CSA events).

5. Conclusions

The results of the present study demonstrate that CSA patients with RVHD had a worse baseline cardiac function, enhanced chemosensitivity, and disordered hemodynamic circulation compared with OSA patients with RVHD. CSA was eliminated after CVR; however, there were no post-CVR changes noted in OSA. The elimination of CSA is thought to be associated with the combined effects of improvement of overall cardiac function (fundamental factor), normalized chemosensitivity, and hemodynamics (direct factors).

Funding sources

This study was supported by the Priority Academic Program of Jiangsu Higher Education Institutions (Grants JX10231801) and Jiangsu Provincial Department of Education (Grants CXLX12_0557).

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.02.007.

References

[1] Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Topfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail 2007;9:251–7.
[2] Hanly PJ, Zuberi-Khokhar NS. Increased mortality associated with Cheyne–Stokes respiration in patients with congestive heart failure. Am J Respir Crit Care Med 1996;153:272–6.
[3] Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. Circulation 2003;107:727–32.
[4] Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 2010;122:352–60.
[5] Shah NA, Yaggi HK, Concato J, Mohsenin V. Obstructive sleep apnea as a risk factor for coronary events or cardiovascular death. Sleep Breath 2010;14:131–6.
[6] Takahashi M, Kasai T, Dohi T, Maeno K, Kasagi S, Kawana F, et al. Conversion from predominant central sleep apnea to obstructive sleep apnea following valvuloplasty in a patient with mitral regurgitation. J Clin Sleep Med 2011;7:523–5.
[7] Yasuma F, Hayashi H, Noda S, Tsuzuki M, Tanaka M, Okada T. A case of mitral regurgitation whose nocturnal periodic breathing was improved after mitral valve replacement. Jpn Heart J 1995;36:267–72.
[8] Rubin AE, Gottlieb SH, Gold AR, Schwartz AR, Smith PL. Elimination of central sleep apnoea by mitral valvuloplasty: the role of feedback delay in periodic breathing. Thorax 2004;59:174–6.
[9] Tomcsanyi J, Karlocai K, Papp L. Disappearance of periodic breathing after heart operations. J Thorac Cardiovasc Surg 1994;107:317–8.

[10] Collop NA. Cheyne–Stokes ventilation converting to obstructive sleep apnea following heart transplantation. Chest 1993;104:1288–9.
[11] Mansfield DR, Solin P, Roebuck T, Bergin P, Kaye DM, Naughton MT. The effect of successful heart transplant treatment of heart failure on central sleep apnea. Chest 2003;124:1675–81.
[12] Abe H, Takahashi M, Yaegashi H, Eda S, Kitahara H, Tsunemoto H, et al. Valve repair improves central sleep apnea in heart failure patients with valvular heart diseases. Circ J 2009;73:2148–53.
[13] Javaheri S, Corbett WS. Association of low $PaCO_2$ with central sleep apnea and ventricular arrhythmias in ambulatory patients with stable heart failure. Ann Intern Med 1998;128:204–7.
[14] Naughton M, Benard D, Tam A, Rutherford R, Bradley TD. Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. Am Rev Respir Dis 1993;148:330–8.
[15] Javaheri S. A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 1999;341:949–54.
[16] Xie A, Rutherford R, Rankin F, Wong B, Bradley TD. Hypocapnia and increased ventilatory responsiveness in patients with idiopathic central sleep apnea. Am J Respir Crit Care Med 1995;152:1950–5.
[17] Hall MJ, Xie A, Rutherford R, Ando S, Floras JS, Bradley TD. Cycle length of periodic breathing in patients with and without heart failure. Am J Respir Crit Care Med 1996;154:376–81.
[18] Ding N, Ni BQ, Zhang XL, Huang HP, Su M, Zhang SJ, et al. Prevalence and risk factors of sleep disordered breathing in patients with rheumatic valvular heart disease. J Clin Sleep Med 2013;9:781–7.
[19] Guidelines for the diagnosis of rheumatic fever. Jones Criteria, 1992 update. Special Writing Group of the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young of the American Heart Association. JAMA 1992;268:2069–73.
[20] Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Faxon Jr DP, Freed MD, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the society of cardiovascular anesthesiologists, society for cardiovascular angiography and interventions, and society of thoracic surgeons. J Am Coll Cardiol 2008;52:e1–e142.
[21] American Thoracic Society statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–7.
[22] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012;8:597–619.
[23] Schulz R, Blau A, Borgel J, Duchna HW, Fietze I, Koper I, et al. Sleep apnoea in heart failure. Eur Respir J 2007;29:1201–5.
[24] Chan J, Sanderson J, Chan W, Lai C, Choy D, Ho A, et al. Prevalence of sleep-disordered breathing in diastolic heart failure. Chest 1997;111:1488–93.
[25] Ferrier K, Campbell A, Yee B, Richards M, O'Meeghan T, Weatherall M, et al. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. Chest 2005;128:2116–22.
[26] Ryan CM, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al. Shift in sleep apnoea type in heart failure patients in the CANPAP trial. Eur Respir J 2010;35:592–7.
[27] Vazir A, Hastings PC, Dayer M, McIntyre HF, Henein MY, Poole-Wilson PA, et al. A high prevalence of sleep disordered breathing in men with mild symptomatic chronic heart failure due to left ventricular systolic dysfunction. Eur J Heart Fail 2007;9:243–50.
[28] Sands SA, Edwards BA, Kee K, Turton A, Skuza EM, Roebuck T, et al. Loop gain as a means to predict a positive airway pressure suppression of Cheyne–Stokes respiration in patients with heart failure. Am J Respir Crit Care Med 2011;184:1067–75.